REMARKS

Claims 2, 15, and 17-21 are pending, claims 3-14 and 16 have been canceled and claims 17- 21 have been added. Claims 2 and 15 were rejected. Further examination and reconsideration respectfully are requested in view of the amendment and remarks herein.

Applicant's Statement Making Interview of Record

Kenneth I. Kohn has authorized the undersigned to file the following statement. "Applicants wish to express their appreciation for the courtesies extended Applicants' representatives, Kenneth I. Kohn and Laura Dellal, during a personal interview with Examiner Afremova on October 16, 2008, and during a personal interview with the examiner's supervisor Examiner Weber on October 28, 2008. Mr. Kohn has reviewed the Interview Summaries prepared by the examiners, and believes that the examiners' statements provide a complete and proper recordation of the substance of the interviews."

Explanation of the Amendment to the Claims

In the Interview Summary mailed November 3, 2008, Examiner Weber wrote "The current claim language is just ambiguous enough to be interpreted as open language and thereby encompass the subject matter disclosed in claim 15 of Kornowski." To avoid any ambiguity in the claim language that may be construed as encompassing the subject matter disclosed in claim 15 of Kornowski, applicants have amended claim 15 to recite "wherein the hypoxic BMSC preconditioned media is not populated by bone marrow stem cells incubated under hypoxic conditions to produce the hypoxic BMSC preconditioned media." Claim 15 has been further amended to specify how cardiac function is improved, namely "by enrichment of the damaged tissue and stimulation of cardiac cell repopulation in the damaged tissue." Support for the amendment can be found throughout the specification and claims as filed; see, for example, page 4 lines 23-26, page 8 lines 17-23, page 9 lines 11-12, page 23 lines 5-7, and page 24 lines 19-27.

Explanation of New Claims

In the Interview Summary mailed November 3, 2008, Examiner Weber wrote "It was suggested that clearly closed language 'a produce consisting of the conditioned medium' would close the claim compared to Kornowski's claim 15 ..." Further to the examiner's suggestion, applicants have added new independent claim 17, which recites "preparing a composition ***consisting of*** hypoxic bone marrow stem cell (BMSC) preconditioned media" [emphasis supplied]. No new matter is introduced by claim 17 and its dependent claim 18.

New independent claim 19 includes incubating and harvesting steps in addition to an administering step. The harvesting step recites harvesting the BMSC from the composition to obtain an hypoxic BMSC preconditioned media, which unambiguously distinguishes the claim from Kornowski's claim 15. New claims 20-21 are dependent from claim 19.

Support for new claims 17-21 can be found throughout the specification and claims as filed, as noted for the amendment of claim 15. Additionally, support for new claim 20 may be found, for example, on page 10 lines 9-19.

New claims 17-21 are properly included in this application. In the Office action mailed December 20, 2005, the examiner issued a restriction requirement. In response to applicant's request, the examiner reconsidered the restriction requirement and rejoined the Group III claims (claims 6-7) with the elected Group 1 claims (claims 1-2). The claims of Groups I and III have an administering step in common. In a Second Preliminary Amendment filed with the RCE mailed December 15, 2006, applicants added new claim 15 which included steps for preparing the media along with an administering step. This claim was examined. Since the new claims 17-21 also have an administering step in common with pending claims 2 and 15, and has additional preparation steps like claim 15 which was examined after its introduction in the Second Preliminary Amendment, applicants believe that the new claims are within Groups I and III and should be examined along with pending claims 2 and 15.

The Rejection of Claims 2 and 15 under 35 U.S.C. § 112 is Overcome by Amendment

Claim 15 stands rejected under 35 U.S.C. § 112 as being indefinite because it does not clearly point out what are active steps of the claimed method. In response, Applicants have amended claim 15 to clarify that "improving cardiac function" is not an active step, but rather is due to "enrichment of the damaged tissue and stimulation of cardiac cell repopulation in the damaged tissue," which is a property of the hypoxic BMSC preconditioned media upon administration into damaged tissue per the active administering step. Support can be found on page 6 lines 11-24 and on page 8 lines 14-26.

Claim 2 stands rejected under 35 U.S.C. § 112 as being indefinite because of lack of antecedent basis for "the products." Applicants have corrected antecedent basis by replacing "products" with "hypoxic BMSC preconditioned media." Claim 2 has further been amended by modifying the phrase "directly to the heart at a specific location of an injury" in response to Examiner Weber's comment in the Interview Summary mailed November 3, 2008, that "clarification of 'intracoronary' and 'directly to the heart' in claim 2 are different would be obtained." Support for this change may be found on, for example, page 9 lines 11-21.

Reconsideration of the rejection of claims 2 and 15 under 35 U.S.C. § 112 is respectfully requested.

Claims 2 and 15 As Amended Are Not Obvious Over Kornowski et al., Hamamano et al., and McIntosh et al.

Claims 2 and 15 were rejected under 35 USC § 103 as being obvious over U.S. Patent No. 7,097,832 (Kornowski, et al.), Hamano, et al. (Cell Transplantation, 9:439-43, 2000) and U.S. Patent No. 6,368,636 (McIntosh, et al.). The rejection is traversed for claims 2 and 15 as amended.

Examiner Weber wrote in the Interview Summary mailed November 3, 2008, that "The current claim language is just ambiguous enough to be interpreted as open language and thereby encompass the subject matter disclosed in claim 15 of Kornowski." To avoid any ambiguity in the claim language that may be construed as encompassing

the subject matter disclosed in claim 15 of Kornowski, applicants have amended claim 15 to recite "administering hypoxic bone marrow stem cell (BMSC) preconditioned media into damaged tissue of the heart, wherein the hypoxic BMSC preconditioned media is not populated by bone marrow stem cells incubated under hypoxic conditions to produce the hypoxic BMSC preconditioned media."

An important distinction between Kornowski and the present invention is the hypoxic BMSC preconditioned media, which is not populated by BMSCs incubated under hypoxic conditions to produce the media. In the Office action, the examiner cites several passages from Kornowski. However, none of these discloses hypoxic BMSC preconditioned media that is not populated by BMSC's incubated under hypoxic conditions to produce the media.

One of the Kornowski passages is at column 15, lines 56-60, which states, "The autologous bone marrow and/or bone marrow products are injected into heart muscle...." Neither term is defined in Kornowski, so their meaning is determined by the understanding of one of ordinary skill in the art. The term "bone marrow" would be understood as the soft red or yellow fatty tissue that fills the central cavities of bones. The term "bone marrow products" would be understood as the individual products found in bone marrow, such as bone marrow cells (including bone marrow stem cells), and soluble factors in bone marrow such as growth factors. While this passage discloses injecting bone marrow and/or bone marrow products into heart muscle, there is no suggestion to inject hypoxic BMSC preconditioned media, as hypoxic BMSC preconditioned media is not a "bone marrow product" as the term is used in Kornowski.

In the interview summary of October 28, and in the Office action, the examiner also stated that the language of claim 15 may encompass the subject matter in claim 15 of Kornowski. This is not so. Kornowski claim 15 depends ultimately from claim 1 (through claims 12 and 10), and therefore discloses administering autologous bone marrow aspirate to sites in the heart or limb. Amended claim 15 at issue recites the administration into damaged tissue of the heart of hypoxic BMSC preconditioned media, which is not populated by bone marrow stem cells incubated under hypoxic conditions to produce the hypoxic BMSC preconditioned media. Kornowski claim 15 does not disclose

administering hypoxic BMSC preconditioned media, and pending amended claim 15 does not contain any limitation of administering bone marrow aspirate.

In the Office action, the examiner also cited the passage from Kornowski at column 17 lines 7-15, which states, "This procedure will involve ... bone marrow harvesting and processing, followed by the use of the autologous bone marrow or its elements (growth factors and/or cellular elements being isolated from the patient's own bone marrow), with or without any ex-vivo stimulation of its delivery forms, to be injected into ischemic or non ischemic myocardium..." This passage does not describe or suggest the use of hypoxic BMSC preconditioned media not populated by BMSC incubated under hypoxic conditions to produce the hypoxic BMSC preconditioned media. While the passage does state that "elements of bone marrow" may be used, the term "elements of bone marrow" is defined as "growth factors and/or cellular elements being isolated from the patient's own bone marrow." The passage continues by stating that the isolated elements may be used with or without ex-vivo stimulation. If the isolated element is a growth factor, ex-vivo stimulation, even assuming exposure to hypoxic conditions, would not change the growth factor or produce more growth factor. If the isolated element is cells, the cells may be exposed to ex-vivo stimulation before injection but it would be those exposed cells that would be injected. This passage of Kornowski has nothing to do with administration of hypoxic BMSC preconditioned media not populated by BMSC incubated under hypoxic conditions to product the hypoxic BMSC preconditioned media.

In summary, the present invention is distinguished from Kornowski, because Kornowski discloses a method of treating cardiac disease by administering autologous bone marrow or its products. In general, and specifically as stated above, Kornowski does not suggest in any way administering hypoxic BMSC preconditioned media not populated by BMSCs incubated under hypoxic conditions to produce the media.

The Examiner cites Hamano et al. for its teaching of the culture of bone marrow cells under hypoxic conditions to enhance production of VEGF and bFGF, and for its discussion of specific hypoxic conditions. However, Hamano et al. discloses the implantation of bone marrow cells to induce angiogenesis, and does not describe or suggest the use of hypoxic BMSC preconditioned media to promote angiogenesis or to

treat diseased hearts. As such, Hamano, et al., either alone or in combination with Kornowski and/or McIntosh, does not render claims 15 and 2 obvious under 35 U.S.C. § 103.

The Examiner also cites McIntosh et al. (U.S. Patent No. 6,368,636). However, McIntosh et al. describes culturing mesenchymal stem cells (MSC) under normoxic conditions and not hypoxic conditions, and using the supernatant from the cells cultured under normoxic conditions to reduce an immune response in transplant recipients. McIntosh does not render claims 15 and 2 obvious because there are a number of differences between McIntosh and the present invention. These include the lack of hypoxic conditions to produce the MSC supernatant, and the absence of any suggestion of improving cardiac function by enrichment of the damaged tissue and stimulation of cardiac cell repopulation in the damaged tissue.

Furthermore, neither Kornowski et al., McIntosh et al., nor Hamano et al., alone or in combination with one or both of the others, renders claims 2 and 15 obvious under 35 U.S.C. § 103(a). None of these references, alone or in combination, suggests administering to a diseased heart hypoxic BMSC preconditioned media not populated by BMSC's incubated under hypoxic conditions to produce the media. The teaching of Kornowski et al. and Hamano et al. that hypoxic culture conditions enhances the production of angiogenic factors does not lead to claims 2 and 15 of the present invention. Indeed, both Kornowski et al. and Hamano et al. ***administer cells and NOT hypoxic preconditioned media from the cells***. Both teach that the cells secrete the factors that promote angiogenesis or may be used for treating ischemic hearts, and explicitly teach that it is the cells which are administered so that when the cells are in the hypoxic environment of the body; they can secrete the factors over time.

Adding the teachings of McIntosh et al. to Kornowski et al. and/or Hamano et al. does not render claims 2 and 15 obvious. McIntosh teaches the use of supernatants from cultured mesenchymal stem cells to reduce the immune response in transplant recipients. The stem cells are cultured under normoxic conditions, not hypoxic, and the supernatants are used to treat rejection in transplant recipients by reducing an immune response, and not to treat a diseased heart by administering hypoxic BMSC preconditioned media into damaged tissue of the heart, wherein the media is

therapeutically effective for improving cardiac function by enriching the damaged tissue and stimulating repopulation of cardiac cells in the damaged tissue.

Conclusion

In view of clear distinctions over Kornowski et al., Hamano et al., and McIntosh et al., each alone or in combination with the others, applicants believe that the application is now in condition for allowance, and respectfully requests favorable reconsideration and the timely issuance of a Notice of Allowance. If a telephone conference would be helpful in resolving any issues concerning this communication, the examiner is invited to contact the undersigned at the phone number set forth below.

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